K120136

510(K) SUMMARY
Summary of Safety and Effectiveness Information
Supporting a Substantially Equivalent Determination

SEP 26 2012

Submitted by: ORIGIO a/s
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Date Prepared: 2012.Sep.19

Device Identification
Trade Name: EmbryoGen® (Cat. No. 1203)

Classification Name: Reproductive media and supplements (21 CFR 884.6180, Product Code MQL)

Predicate Device
EmbryoAssist (K080473)

Description
EmbryoGen® is designed to provide physiological conditions for the embryo from fertilization to Day 3 at the time when the embryo under in vivo conditions would be transported through the oviduct.

EmbryoGen® is based on the FDA-cleared culture media EmbryoAssist™ (K080473) supplemented with Leukine (sargramostim) GM-CSF.

EmbryoGen® is supplied in sterilized transparent glass bottles with polypropylene screw top closure in a volume of either 3 mL or 5 mL.

The media is colorless, sterile and ready to use by professionals for assisted reproduction. EmbryoGen® is quality control tested before release for pH, sterility, Mouse Embryo Assay, endotoxin, osmolality, GM-CSF concentration (by ELISA), GM-CSF potency (TF-1 cell assay) and HSA concentration (by ELISA).

Indication for use
EmbryoGen® is for fertilization and culture until the 2-8 cell stage.
EmbryoGen® can also be used for embryo transfer at day 2 or 3.

Technological Characteristics
EmbryoGen® supports the development and cell division of human embryos. Embryos, which have been exposed to EmbryoGen®, are transferred to the woman's uterus, where they potentially implant and result in a pregnancy.

The technological characteristics of EmbryoGen® are essentially similar to the predicate device EmbryoAssist™ (K080473). They have the same intended use and the same components. The only difference is addition of GM-CSF to EmbryoGen®.

EmbryoGen® is considered to be functionally equivalent to the predicate device, and is subject to the same quality control tests before release. Further to this a GM-CSF TF-1 cell Assay and an ELISA test are also conducted:
Test on sterility, osmolality, 1-cell Mouse Embryo Assay, pH, Endotoxin, TF-1 cell assay, GM-CSF ELISA and HSA concentration.
Therefore, EmbryoGen® is considered substantially equivalent to the predicate device EmbryoAssist (K080473).

Performance and safety data
Clinical Study:
To evaluate the efficiency and safety of EmbryoGen® on human embryos, a multicenter, randomized, parallel group, double-blind, placebo-controlled clinical study with adaptive design was conducted at 14 study centers. A total of 1,332 subjects were enrolled/randomized (ITT-population), and of these 1,149 were counted as the PP-population. The objective of this study was to assess whether addition of 2 ng/mL GM-CSF to the embryo culture medium EmbryoAssist™ would significantly increase the chance of a pregnancy after in vitro fertilization. The primary endpoint was ongoing implantation rate at gestational week 7, evaluated by ultrasound scan. The study hypothesis was to demonstrate a 25% relative increase in ongoing implantation rate at gestational week 7, after fertilization, culture until day 3 and transfer in the presence of 2 ng/mL GM-CSF compared to fertilization, culture and transfer in EmbryoAssist™. Secondary endpoints were to assess whether a GM-CSF effect was measurable on embryo quantity and quality parameters, evaluated as number of top quality embryos and number of normally developed day 3 embryos judged against predefined classification. Follow-up was based on data until gestational week 12 and birth data (including abnormalities/malfunctions) retrieved from the Danish National Board of Health Register (93%) supplemented with data from a follow-up questionnaire returned by the patient/couple (7%).

Selection criteria for subject enrolment were the following: Women referred for standard IVF/ICSI treatment, who agreed to participate in the study and to have their oocytes cultured with or without 2 ng/mL GM-CSF. All women were aged 25-39 years (both inclusive) and characterized by having a regular menstrual cycle, standard GnRH agonist or antagonist protocol, FSH/hMG starting dose between 100 and 300 IU daily, at least 3 follicles with a calculated diameter of ≥14 mm at the day of hCG, and including a leading follicle of minimum 17 mm.

All subjects in the PP-population had their oocytes fertilized and the resulting zygotes/embryos cultured until day 3 and transferred using the allocated study medium. An interim analysis was performed after recruitment of 355 eligible subjects, counting 301 women in the PP-population with embryo transfer and reported data until gestational week 7. The interim analysis did not result in any change of inclusion/exclusion criteria or hypothesis, but was used for sample size adjustment. Also, because suboptimal performance of the control medium was evident at interim analysis, the concentration of HSA was increased from 2 to 5 mg/mL in both control and GM-CSF test medium just over halfway through the treatment cohort, after 620 includable women with embryo transfer. This alteration increased the ongoing implantation rate gestational week 7 for the control group from 17.9% to 22.4%, but did not affect performance of the GM-CSF medium (23.9% and 23.0% in low and high HSA concentration medium, respectively). 5 mg/mL HSA (0.5%) is the standard concentration used in ART culture media.

The overall results showed an ongoing implantation rate gestational week 7 (primary endpoint calculated for the PP-population) of 23.5% for women in the GM-CSF group, and 20.0% for women in the control group, which was not statistically significant (p=0.17). However, the results did show a statistical significant difference in gestational week 12 and Live Birth: ongoing implantation rate week 12 was 23.0% for women in the GM-CSF group versus 18.7% in the control group (p=0.02) and Live Birth rate 28.9% versus 24.1% (p=0.03). However, this was primarily attributable to suboptimal performance of the control medium containing a low concentration of HSA.

The secondary endpoints in the study were number of top quality embryos and normally developed day 3 embryos. No effect of GM-CSF was found with regard to the quantity of embryos fulfilling these embryo quality parameters.

Based on follow-up data, live birth and baby health characteristics for the full study cohort, including AE/SAE reports received until gestational week 12, there are no indications of any unacceptable clinical risks when adding 2 ng/mL GM-CSF to the culture medium.

In a predefined subgroup of women who had previously experienced at least one miscarriage (spontaneous abortion) (n=289 patients with embryo transfer), addition of GM-CSF had a significant effect on ongoing implantation rate gestational week 7 (24.5% [GM-CSF] vs. 17.0% [control] (p=0.001)). This effect was seen in the presence of both low (27.3% [GM-CSF]) and high (21.2% [GM-CSF]) HSA concentration. Raising the HSA concentration did not have any impact on control values within this subgroup, with ongoing implantation rates gestational week 7 of 17.4% (low HSA) vs. 16.3% (high HSA). Live birth rate per woman with an embryo transfer was 29.6% (GM-CSF) vs. 23.1% (control) (p=0.02).

In conclusion, we have demonstrated a modest effect of GM-CSF on ongoing implantation rate and live birth rates in unselected women undergoing IVF treatment when compared to a control medium. This positive effect was primarily evident in a culture medium containing 2 mg/mL HSA and disappeared when the concentration of HSA was increased to 5 mg/mL. However, GM-CSF increased ongoing implantation rate, clinical pregnancy and live birth rate in a subgroup of women who had experienced previous miscarriage (~25% of the full study cohort), regardless of HSA concentration. Furthermore, this study, with a total of 369 babies born, also showed that culture medium supplemented with 2 ng/mL GM-CSF was no worse than control medium regarding miscarriages and babies born with abnormalities/malfunctions.

Literature:
Published studies have shown that supplementing culture media for IVF with 2 ng/ml recombinant GM-CSF results in better quality embryos, potentially leading to higher implantation and pregnancy rates. Other studies report lack of an effect of GM-CSF, whereas no inhibitory effects of GM-CSF have been reported when adding 2 ng/mL, which is the concentration of GM-CSF in EmbryoGen®. The safety of supplementing the culture medium with 2 ng/mL GM-CSF was examined, and a thorough investigation showed that the chromosomal constitution in humans was no worse in the group of women having their oocytes fertilized and embryos cultured in the presence of 2 ng/mL GM-CSF compared with the control group (Agerholm I, Loft A, Hald F, Lemmen JG, Munding B, Sorensen PD, Ziebe S.: Culture of human oocytes with granulocyte-macrophage colony-stimulating factor has no effect on embryonic chromosomal constitution. Reprod Biomed Online. 2010;20:477-484).

Overall conclusion:

The conclusion from the performance and safety data, intended use comparison, product formulation comparison and test specification comparison as well as the nonclinical data demonstrates that the EmbryoGen® is suitable for its intended use, and meets the criteria in the comparison to predicate device (EmbryoAssist, K080473) in which substantial equivalence has been demonstrated, and meets the criteria outlined in the Notice of Final Rule, 63 FR 48428, Docket Number 97N-0335.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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SEP 26 2012

Re: K120136
Trade/Device Name: EmbryoGen®
Regulation Number: 21 CFR§ 884.6180
Regulation Name: Reproductive media and supplements
Regulatory Class: II
Product Code: MQL
Dated: September 12, 2012
Received: September 13, 2012

Dear Dr. Gruff:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical

device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Benjamin R. Fisher, Ph.D.
Director
Division of Reproductive, Gastro-Renal,
and Urological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

Indication for Use

510(k) Number (if known): (Not yet assigned) K120136

Device Name:

EmbryoGen®

Indication for Use:

EmbryoGen® is for fertilization and culture until the 2-8 cell stage.
EmbryoGen® can also be used for embryo transfer at day 2 or 3.

Prescription Use ___X___ AND/OR Over-The-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

25 Sept 2012

(Division Sign-Off)
Division of Reproductive, Gastro-Renal, and Urological Devices
510(k) Number K120136